DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 21-526 (Ranexa; ranolazine for angina)

Sponsor: CV Therapeutics

Review date: 29 September 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: This is a secondary review of Ranexa, ranolazine for angina.

Distribution: NDA 21-526
HFD-110/Project Manager
HFD-110/Gordon/Hausner/Koerner/Targum
HFD-710/Freidlin/Hung
HFD-810/Chidambaram
HFD-860/Bhattaram/Hinderling/Nguyen

This secondary review is based on primary reviews of chemistry (Dr. Chidambaram, 15 September 2003), pharmacology and toxicology (Dr. Hausner, 2 September 2003; Dr. Koerner, 4 September 2003), clinical pharmacology and biopharmaceutics (Drs. Hinderling, Nguyen, and Bhattaram, 15 September 2003), clinical efficacy (Drs. Targum and Freidlin, 28 August 2003, 2 September 2003, and 12 September 2003), and clinical safety (Dr. Gordon, 31 July 2003).

An NDA amendment submitted on 13 September 2003 was considered by all primary reviewers and it was found not to make a material contribution to the issues raised by those reviewers.

From a manufacturing perspective, Ranexa should be considered approvable, pending (since 14 January 2003) the results of the inspection of the manufacturing facility.

The mechanism by which ranolazine may be antianginal is unclear. The sponsor's preclinical studies suggest it may be through inhibition of cardiac metabolism of fatty acids. Ranolazine and its metabolites interact with various cardiac ion channels, including IKr and IKs. Ranolazine prolongs the action potential duration in cardiac M-cells. In the ventricular wedge, ranolazine prolongs the transmural QT interval and slows the action potential upstroke, in the presence of hypokalemia, at concentrations similar to what may be effective in man. Early afterdepolarizations were not seen.[1]

Ranolazine produces embryotoxicity in rats and rabbits and skeletal malformations in fetal rats, at doses well below that shown to be effective in man.

Ranolazine is a racemate. The plasma level peaks 2 to 5 hours after multiple doses of the sustained-release formulation. Absorption is about 73% from an aqueous solution. Bioavailability of the tablet is 76% of that from a solution. Bioavailability of ranolazine is unaffected by food. As shown in Table 1, AUC increases somewhat more than linearly

[1] *Dr. Koerner's review cites additional shortcomings of available preclinical data related to proarrhythmic risk. Ranolazine was not studied in the ventricular wedge preparation under conditions necessary to elicit cisapride's proarrhythmia. Metabolites have not been adequately studied. Ranolazine has also not been evaluated in the presence of other risk factors for proarrhythmia, including female gender, pacing with a pause or with an accelerating rhythm, with adrenergic stimulation, or with heart failure.*

after multiple doses. Variability is high; the CV is about 50 to 80% for estimates of Cmax and AUC. With repeated dosing, ranolazine levels increase by less than two-fold.

Table 1. Single- and multiple-dose pharmacokinetics[2]

	500 mg	1000 mg	1500 mg
AUC day 1	9615	21075	33779
AUC day 6	13720	32902	56134

There must be substantial binding of ranolazine in tissues, since binding to plasma protein and erythrocytes do not account for ranolazine's large volume of distribution (>80 L).

Ranolazine is extensively metabolized with pathways involving CYP 3A4, CYP 2D6, sulfatases, and glucuronidases. Four "major" circulating metabolites have AUCs 5 to 40% of the AUC for ranolazine. Elimination of radioactivity after oral administration of labeled ranolazine in solution is by urine (73%) and feces.

Ketoconazole increases plasma levels of ranolazine by about 3-fold. Common doses of diltiazem (up to 360 mg QD studied) increase ranolazine levels 2.8-fold. The 2D6 inhibitor paroxetine had relatively small effects. Digoxin levels increased 40 to 70% after to-be-marketed doses of ranolazine.

Of the 80-some studies reported, only two have been identified as useful to characterize the effectiveness of sustained-release ranolazine in angina.

The first such study is CVT3033, a randomized, double-blind, parallel, and placebo-controlled study. Active study groups received 750 or 1000 mg BID for 12 weeks. Exercise testing (treadmill with modified Bruce protocol) was performed at "peak" (4 hours after dosing) at weeks 2 and 12, and "at trough" at weeks 2, 6, and 12. A final assessment for "rebound" was conducted 48 hours after the last dose. Subjects in this study were on a background of amlodipine 5 mg QD or diltiazem 180 mg QD[3].

The principal measures of effectiveness are shown in Table 2 and Table 3 below.

Table 2. Effectiveness in CVT3033[4]

Change from baseline. placebo	750 mg BID		1000 mg BID	
	Peak	Trough	Peak	Trough
Total ETT (s)	34±11	24±11	26±11	24±11
Onset angina	38±12	30±12	38±13	26±12
1 mm ST depression	41±12	29±12	35±12	21±12

Table 3. Angina during CVT3033.

Angina/week	Placebo	750 mg	1000 mg
Baseline	4.6±0.4	4.4±0.3	4.4±0.3
Double-blind	3.3±0.3	2.5±0.2	2.1±0.2

The primary end point treatment effect at trough is only marginally significant (0.03 for each dose), so the statistical significance is quite sensitive to various robustness

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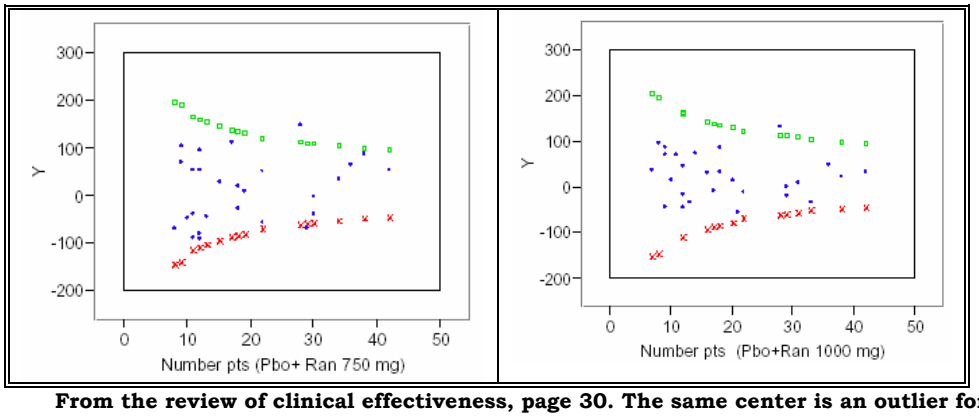
[2] *Adapted from the review of clinical pharmacology, page 120.*

[3] *Such a background cannot be considered responsive to the need to demonstrate effectiveness in a refractory population.*

[4] *Adapted from the review of effectiveness, page 8.*

exercises, such as exclusion of the "outlier" site in the funnel plot shown in the figure below.



From the review of clinical effectiveness, page 30. The same center is an outlier for the analysis of results on 750 mg (left) and 1000 mg (right), perhaps because what is discrepant is the placebo effect.

Drs. Targum and Freidlin also evaluated various subgroups within this study, but the marginal overall results doomed this effort.

While it remains unclear what combination of factors contributed to difficulties in obtaining a robust effect in CVT3033—effect size, inter-subject variability, inter-center variability, dosing interval—the two doses, producing, as they do, plasma levels that overlap considerably, support one another for the primary end point of total exercise time, for secondary end points of time to onset of angina and time to ST depression, and for the rate of angina attacks. Furthermore, effects on exercise time were, as would be expected, somewhat larger, and certainly statistically more robust when assessed nearer the time of peak plasma levels.

The second study supporting effectiveness is CVT3031, a randomized, double-blind study in which subjects not on background antianginal therapy received, in random order, one week on placebo and ranolazine 500, 1000, and 1500 mg BID. This study had one baseline assessment (ETT based on the modified Bruce protocol), and then single ETT assessments at the end of each crossover period. There was no washout between crossover periods.

Again, for reasons not well understood, the results are not very compelling. In addition to the sample-size issues raised by study CVT3033, CVT3031 adds concerns related to carryover effects (which, given the short half life, were not expected) and training effects.

Table 4. Effectiveness in study CVT3031[5]

	500 mg BID		1000 mg BID		1500 mg BID	
	Peak	**Trough**	**Peak**	**Trough**	**Peak**	**Trough**
Total ETT	29±7	23±8	52±7	35±9	56±8	46±9
Onset angina	34	31	57	35	70	60
1 mm ST	38	24	60	44	66	66

And, as in CVT3033, larger and more statistically significant results are seen in measurements of exercise near the time of peak plasma levels.

[5] *Adapted from sponsor's study report, vol 1.146, page 311ff. Time to onset of angina and time to ST depression were not reported in the primary review.*

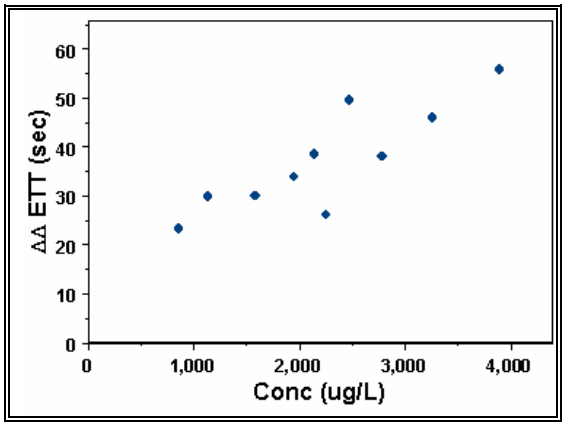
These studies—and there really are no others suitable for evaluating the effects of sustained-release ranolazine on exercise—are subject to some fair criticism. In particular, they failed to demonstrate a dose-response relationship, because the doses were close together and the intersubject variability in plasma levels was large within a dose group. Thus, one can consider at least adjacent dose groups within these studies as multiple looks at nearly the same dose. As such, the results are entirely internally consistent—active drug was always better than placebo on total exercise time and time to onset of angina and time to 1-mm ST depression, all true for measurements at the interdosing interval as well as "peak".

Some consideration has been given to whether the less impressive results at the interdosing interval were the result of getting the interdosing interval wrong. However, looking at the nominal trough-peak ratio for values shown in Table 2 and Table 4 reveals a fairly consistent estimate >0.5, as shown in Table 5[6].

Table 5. Nominal trough-peak ratios in studies CVT3033 and CVT3031.

	CVT3033		CVT3031		
	750 mg	**1000 mg**	**500 mg**	**1000 mg**	**1500 mg**
Total ETT	0.71	0.92	0.79	0.67	0.82
Onset angina	0.79	0.68	0.91	0.61	0.86
ST depression	0.49	0.60	0.63	0.73	1.00

Additional evidence of a relationship of ETT to dose comes from pharmacometric analyses of ETT by peak and trough plasma levels in these two studies, shown in the figure below.

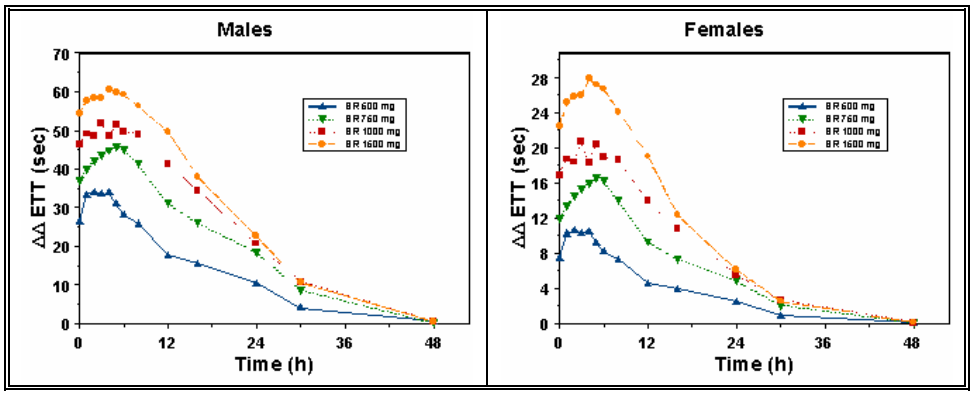


From the review of clinical pharmacology, page 307.

The pharmacometrics team modeled the relationship between plasma levels and ETT and the time course of plasma levels to obtain expected treatment effects as a function of time, as shown in the figure below[7].

[6] *However, it must be said that there are no data adequately describing the time course of treatment effect. In particular, the "peak" measurements were made earlier than the estimated time of peak plasma concentrations. The effect of underestimating the true peak effect is that the trough-peak ratios will be inflated.*

[7] *However, to be clear, there are no data for times other than "peak" and interdosing interval.*



From the review of clinical pharmacology, page 310.

Note that the effect in women follows the same time course as the effect in men, but that the effect size is about half as large. This difference is not the result of differences in pharmacokinetics.

The sponsor[8] has suggested that Study Ran-072[9] is supportive of a treatment effect in a refractory population. This was a randomized, double-blind, two-period crossover study in which subjects with chronic angina on beta-blockers (n=61, up to 100 mg QD of atenolol or metoprolol), calcium channel blocker (n=43, up to 60 mg QID of diltiazem), or both (n=50) received treadmill exercise tests 2.5 to 3 hours following placebo and single oral doses of ranolazine 10, 60, 120, or 240 mg. Some of the results of this study (abstracted from the clinical review) are shown in Table 6.

Table 6. Change in total ETT (Ran-072).

	Ranolazine + BB				Ranolazine + CCB				Both	
	10 N=14	60 N=15	120 N=17	240 N=15	10 N=10	60 N=11	120 N=12	240 N=10	10 N=24	60 N=26
ΔETT	7	21	5	39*	12	6	-8	34	10	14
*Nominal p=0.02										

The subjects in this study were not shown to be resistant to other therapy, nor was the other therapy optimized for each subject. The doses of ranolazine in this study were lower than those explored in later studies, so it is not surprising that no treatment effect is seen, even near the time of peak plasma levels of ranolazine—no evident dose-response and no statistically significant treatment effect after correction for 10 possible comparisons. This study does not support effectiveness of ranolazine in a resistant population.

In total, nearly 2700 subjects were exposed to ranolazine in more than 80 clinical studies. Much of this, however, was with short-term exposure, doses lower than are now believed to be effective, and with the immediate-release formulation. About 750 subjects received at least one dose of sustained-release ranolazine at a dose of 500 to 1500 mg BID for an average of about 10 weeks. Several hundred subjects received open-label ranolazine for more than one year.

During controlled studies, subjects receiving ranolazine were, compared to those receiving placebo, more likely to experience adverse events, more likely to have adverse

[8] *Personal communication.*

[9] *Medical/statistical review page 47.*

events considered severe, causing a reduction, interruption, or discontinuation of treatment, or associated with a fatal outcome.

Category	Number (%) of Subjects/Patients			
	ISS Database		Phase 2/3 SR Controlled Studies	
	Total Ranolazine (N = 2,682)	All Placebo (N = 1,529)	Total Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	160	25	66	53
Any AE	1,465 (54.6)	418 (27.3)	275 (36.7)	101 (22.2)
Any SAE	255 (9.5)	30 (2.0)	51 (6.8)	16 (3.5)
Any Severe AE	286 (10.7)	47 (3.1)	46 (6.1)	14 (3.1)
Any Possibly/Probably Drug-Related AE	852 (31.8)	182 (11.9)	140 (18.7)	26 (5.7)
Any AE Leading to Death	23 (0.9)	3 (0.2)	4 (0.5)	3 (0.7)
Any AE Leading to Dose Reduction	48 (1.8)	1 (0.1)	0	0
Any AE Leading to Dose Interruption	70 (2.6)	8 (0.5)	23 (3.1)	3 (0.7)
Any AE Leading to Study Drug Discontinuation	210 (7.8)	28 (1.8)	60 (8.0)	17 (3.7)
Any AE Leading to Adding Concomitant Medication	646 (24.1)	136 (8.9)	112 (15.0)	45 (9.9)

AE = adverse event; SAE = serious adverse event

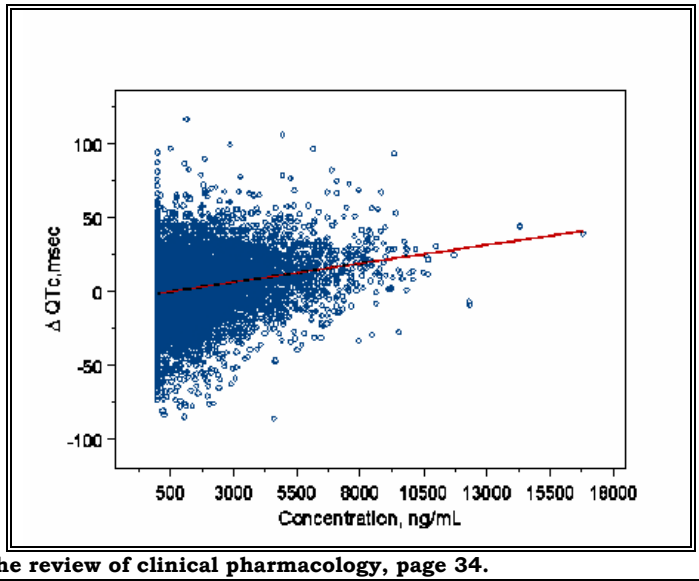
Abstracted from **Appendix III B Table E-1.1, Appendix V B Table E-1.3, Appendix III D Table G-1.1,** and **Appendix V D Table G-1.3**.

From the review of clinical safety, page 15.

During controlled studies, the most common adverse events, more common on ranolazine than placebo, were dizziness (8% vs. 1%), constipation (7% vs. <1%), and nausea (6% vs. <1%).

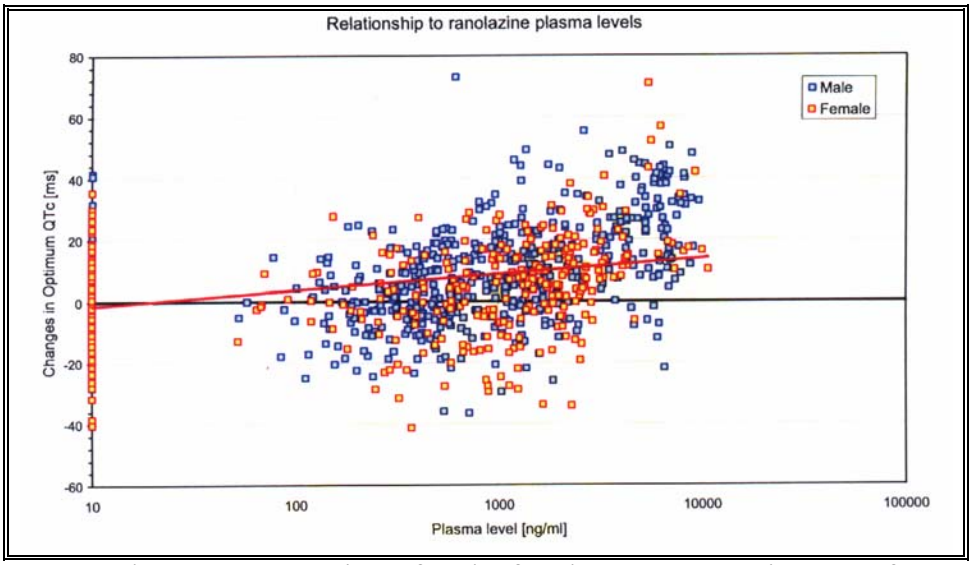
There were 37 deaths during the development program (33 on ranolazine). These were mostly cardiovascular, with some described only as sudden. Two subjects, both on ranolazine 1000 mg BID had sudden deaths long after reported QTc values >500 ms.

As shown in the figure below, the change in QTc was positively correlated with plasma levels of ranolazine.



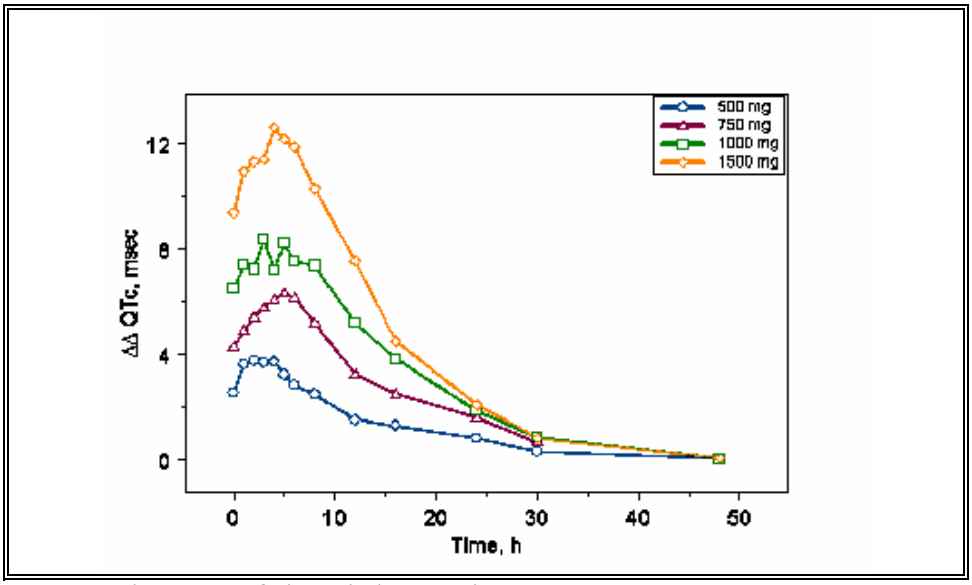
From the review of clinical pharmacology, page 34.

However the nonlinearity of the relationship between QT and dose and the steepness with which QTc increases with plasma levels >1000 ng/mL is better illustrated in data taken solely from the ketoconazole study.



From the sponsor's re-analysis of study of study CVT 301-10; submission of 13 September 2003, vol 8, section 8.3.1, page 11. The report asserts that a curvilinear fit to these data is not superior to a linear fit. However, the vast majority of data points at plasma levels >1000 ng/mL are above the fitted line, and the vast majority of points at plasma levels <1000 ng/mL are below the fitted line.

The (linear) model-based estimated time course of changes in QTc is shown in the figure below.



From the review of clinical pharmacology, page 35.

Ranolazine has no effect on heart rate. Effects of ranolazine on QTc were manifest in controlled studies[10], modeled in the figure above. The mean double difference from baseline and placebo was, at peak, about 4 ms at 500 mg BID, increasing monotonically

[10] *Values shown are Bazett-corrected QT. Where Fredericka-corrected data are available, the trends are similar.*

with dose, to about 12 ms at 1500 mg BID. At the highest dose, 6% of subjects reported changes from baseline >60 ms and 7.5% had QTc >500 ms[11].

The difference between the linear and nonlinear models is of little consequence for doses up to 1500 mg in the absence of metabolic inhibition. However, in the presence of metabolic inhibition, the linear model grossly underestimates the effect on the QTc near the time of peak plasma level.

Notched T waves were also more likely to be reported on drug than on placebo. The incidence increased with dose and, within dose, by plasma level. At 10,000 ng/mL, the likelihood of notched T-waves was about 75%. The clinical significance of this is not clear.

Ranolazine appears to be conventional with respect to its effects on angina, conventional in the nature of its benefits (symptomatic), conventional in the magnitude of its benefits (modest), and conventional with respect to most aspects of its safety profile.

Ranolazine's most distinguishing feature is its effect on ventricular repolarization, seen in preclinical assessments, mean effects on QTc, and outliers for QTc. Despite the less-than-linear increase in plasma levels with dose, effects on QT, unlike effects on ETT, were fairly easily distinguished by dose. This suggests that QT prolongation can be attenuated by keeping the dose below 1000 mg BID. However, large inter-subject variability in pharmacokinetics and drug interactions involving 3A4 inhibitors, 2D6 inhibitors, diltiazem, and digoxin will clearly undermine efforts to control the risks by limiting dose. Available clinical data do little to constrain the estimated rate of arrhythmias that may result from use of ranolazine; the clinical experience with long-term use is simply too small.

Under the circumstances, restriction of use to a population refractory to usual treatments is the only sensible option. If one understood enough about the mechanism of antianginal action of ranolazine, one might entertain approving this restricted use without a specific study in a refractory population. However, the mechanism is not well understood, and the pharmacodynamic interaction of ranolazine with other antianginal agents cannot be predicted with confidence. Ranolazine should be considered "approvable", pending demonstration of use in a refractory population.

Because of concerns about the effects of ranolazine on ventricular repolarization, at several points in the development program, the sponsor was encouraged to study its use in a population with refractory angina[12].

In a letter to Dr. Throckmorton, dated 5 September 2003, the sponsor reaches much the same conclusion:

> *"It therefore appears reasonable to allow a trial of ranolazine in those patients in whom the currently available agents have been demonstrated to be either inadequate or not tolerated. For those among them whose angina symptoms are decreased by ranolazine, the benefit will surely justify the risk, if any, of the small QT effect."*

This additional study may need to carry some additional burdens. At least, it needs to provide better characterization of the dose-response relationship. Some considerations should also be given to issues relating to effects in subgroups by gender.

Various review disciplines have commented on parts of the proposed label that would need amending. These comments can be gathered into a deficiencies letter, but a

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[11] *In the sponsor's re-analysis of data from two studies, lower rates of outliers are reported when the basis of study is only lead II, rather than all leads. The trend of an increased incidence with dose remains.*

[12] *See Dr. Targum's review of 12 September 2003 for a brief history of the formal interactions with the sponsor.*

complete labeling recommendation is not possible until the results of the missing study are known.